## Frequency of mononuclear diploid cardiomyocytes underlies natural variation in heart regeneration.

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**Public Summary:**

**Scientific Abstract:**
Adult mammalian cardiomyocyte regeneration after injury is thought to be minimal. Mononuclear diploid cardiomyocytes (MNDCMs), a relatively small subpopulation in the adult heart, may account for the observed degree of regeneration, but this has not been tested. We surveyed 120 inbred mouse strains and found that the frequency of adult mononuclear cardiomyocytes was surprisingly variable (>7-fold). Cardiomyocyte proliferation and heart functional recovery after coronary artery ligation both correlated with pre-injury MNDCM content. Using genome-wide association, we identified Tnni3k as one gene that influences variation in this composition and demonstrated that Tnni3k knockout resulted in elevated MNDCM content and increased cardiomyocyte proliferation after injury. Reciprocally, overexpression of Tnni3k in zebrafish promoted cardiomyocyte polyploidization and compromised heart regeneration. Our results corroborate the relevance of MNDCMs in heart regeneration. Moreover, they imply that intrinsic heart regeneration is not limited nor uniform in all individuals, but rather is a variable trait influenced by multiple genes.